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(21) International Application Number: <b>PCT/US99/09847</b>		<p>(US). FLORENCE, Kimberly [US/US]; 12805 Atlantic Avenue, Rockville, MD 20851 (US). NI, Jian [CN/US]; 5502 Manorfield Road, Rockville, MD 20853 (US). ROSEN, Craig, A. [US/US]; 22400 Rolling Hill Road, Laytonsville, MD 20882 (US). CARTER, Kenneth, C. [US/US]; 11601 Brandy Hall Lane, North Potomac, MD 20878 (US). MOORE, Paul, A. [US/US]; 19005 Leatherbark Drive, Germantown, MD 20874 (US). OLSEN, Henrik, S. [DK/US]; 182 Kendrick Place #24, Gaithersburg, MD 20878 (US). SHI, Yang-gu [CN/US]; 437 West Side Drive, Gaithersburg, MD 20878 (US). YOUNG, Paul, E. [US/US]; 122 Beckwith Street, Gaithersburg, MD 20878 (US). WEI, Fing-Fei [CN/US]; 242 Gravatt Drive, Berkeley, CA 94705 (US). BREWER, Laurie, A. [US/US]; Apartment 115, 410 Van Dyke Street, St. Paul, MN 55119-4321 (US). SOPPET, Daniel, R. [US/US]; 15050 Stillfield Place, Centreville, VA 22020 (US). LAFLEUR, David, W. [US/US]; 3142 Quesada Street, N.W., Washington, DC 20015 (US). ENDRESS, Gregory, A. [US/US]; 9729 Clagett Farm Drive, Potomac, MD 20854 (US). EBNER, Reinhard [DE/US]; 9906 Shelburne Terrace #316, Gaithersburg, MD 20878 (US).</p> <p>(74) Agents: BROOKES, A., Anders et al.; Human Genome Sciences, Inc., 9410 Key West Avenue, Rockville, MD 20850 (US).</p> <p>(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZA, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).</p> <p><b>Published</b>  <i>With international search report.</i>  <i>Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</i></p>	
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(71) Applicant (for all designated States except US): HUMAN GENOME SCIENCES, INC. [US/US]; 9410 Key West Avenue, Rockville, MD 20850 (US).			
(72) Inventors; and			
(75) Inventors/Applicants (for US only): RUBEN, Steven, M. [US/US]; 18528 Heritage Hills Drive, Olney, MD 20832			
(54) Title: <b>97 HUMAN SECRETED PROTEINS</b>			
(57) Abstract			
<p>The present invention relates to novel human secreted proteins and isolated nucleic acids containing the coding regions of the genes encoding such proteins. Also provided are vectors, host cells, antibodies, and recombinant methods for producing human secreted proteins. The invention further relates to diagnostic and therapeutic methods useful for diagnosing and treating disorders related to these novel human secreted proteins.</p>			

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:29 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1487 of SEQ ID NO:29, b is an integer of 15 to 1501, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:29, and where b is greater than or equal to a + 14.

### FEATURES OF PROTEIN ENCODED BY GENE NO: 20

Preferred polypeptides of the invention comprise the following amino acid sequence:

GTPAGTGPEFPGRPTRPSRTESAQTTQHSPLRPLWRLKRDSSPCHPQTRADWG  
VCPWGGAAQGLRPGCH  
LAPRRCLCPGSCCPWHWAEAQWSFLWRGLWGLRTLPTALRASPAASGTVTY  
SACLGTSCLLRAPCWRLRT CRQSWC (SEQ ID NO: 275),  
GTPAGTGPEFPGRPTRPSRTESAQTTQH (SEQ ID NO: 276),  
SPLRPLWRLKRDSSPCHPQTRADWGVCPW (SEQ ID NO: 277),  
GGAAQGLRPGCHLAPRRCLCPGSCCPWHWA (SEQ ID NO: 278),  
EAQWSFLWRGLWGLRTLPTALRASPAASGT (SEQ ID NO: 279), and/or  
VTYSACLGTSCLLRAPCWRLRTCRQSWC (SEQ ID NO: 280). Polynucleotides encoding these polypeptides are also provided.

The gene encoding the disclosed cDNA is believed to reside on chromosome 3. Accordingly, polynucleotides related to this invention are useful as a marker in linkage analysis for chromosome 3.

This gene is expressed primarily in osteoarthritis, breast cancer, and uterine cancer, and, to a lesser extent, in brain.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are

not limited to, cancer, particularly breast and uterine cancer; and neurological diseases and/or disorders. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above  
5 tissues or cells, particularly of the breast, lymph node, and CNS, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g., reproductive, breast, skeletal, joint, neural, and cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, amniotic fluid, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an  
10 individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

Preferred epitopes include those comprising a sequence shown in SEQ ID NO: 130 as residues: Gln-75 to Cys-80.

15 The tissue distribution in breast and uterine cancer indicates that the protein product of this gene is useful for the diagnosis and/or treatment of a variety of cancers, particularly breast cancer and uterine cancer. Expression of this gene in brain also indicates that it may play a role in neurological function, and that its absence may lead to disorders such as Alzheimer's & Parkinson's disease. Expression of this gene  
20 product at elevated levels within cancerous tissue indicates that it may be a player in the progression of the disease, perhaps by driving proliferation or blocking differentiation or apoptosis. Therefore, beneficial therapeutics may be developed based upon attempts to block this gene product.

Representative uses are described in the "Hyperproliferative Disorders" and  
25 "Regeneration" sections below and elsewhere herein. Briefly, developmental tissues rely on decisions involving cell differentiation and/or apoptosis in pattern formation. Dysregulation of apoptosis can result in inappropriate suppression of cell death, as occurs in the development of some cancers, or in failure to control the extent of cell death, as is believed to occur in acquired immunodeficiency and certain  
30 neurodegenerative disorders, such as spinal muscular atrophy (SMA). Because of potential roles in proliferation and differentiation, this gene product may have applications in the adult for tissue regeneration and the treatment of cancers. It may

also act as a morphogen to control cell and tissue type specification. Therefore, the polynucleotides and polypeptides of the present invention are useful in treating, detecting, and/or preventing said disorders and conditions, in addition to other types of degenerative conditions. Thus this protein may modulate apoptosis or tissue differentiation and is useful in the detection, treatment, and/or prevention of degenerative or proliferative conditions and diseases. The protein is useful in modulating the immune response to aberrant polypeptides, as may exist in proliferating and cancerous cells and tissues. The protein can also be used to gain new insight into the regulation of cellular growth and proliferation. Furthermore, the protein may also be used to determine biological activity, to raise antibodies, as tissue markers, to isolate cognate ligands or receptors, to identify agents that modulate their interactions, in addition to its use as a nutritional supplement. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:30 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1738 of SEQ ID NO:30, b is an integer of 15 to 1752, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:30, and where b is greater than or equal to a + 14.

25

#### **FEATURES OF PROTEIN ENCODED BY GENE NO: 21**

This gene shares sequence homology with a yeast hypothetical 52.9 KD protein CDC26-YMR31 intergenic region (See Genbank Accession No. gplD50617|YSCCHRVI\_114.). This gene has been mapped to chromosome 18q22-23, and therefore can be used in linkage analysis as a marker for 18q22-23.

30

Gene No.	cDNA Clone ID	ATCC Deposit Nr and Date	Vector	NT SEQ ID NO: X	Total NT Seq.	5' NT of Clone Seq.	3' NT of Clone Seq.	5' NT of Start Codon	5' NT of First AA of Signal Pep	AA SEQ ID NO: Y	First AA of Sig Pep	Last AA of Sig Pep	First AA of Secreted Portion	Last AA of ORF
12	HE2ES51	209745 04/07/98	Uni-ZAP XR	22	1447	1	1447	77	77	122	1	14	15	222
13	HTXDW56	209746 04/07/98	Uni-ZAP XR	23	1583	1	1583	217	217	123	1	22	23	201
14	HEEAG23	209745 04/07/98	Uni-ZAP XR	24	1669	25	1280	57	57	124	1	18	19	46
15	HDPKJ93	209745 04/07/98	pCMVSPORT 3.0	25	1053	1	1053	46	46	125	1	21	22	305
16	HDLAC10	209745 04/07/98	pCMVSPORT 2.0	26	1477	1	1477	132	132	126	1	29	30	81
17	HDPOH06	209745 04/07/98	pCMVSPORT 3.0	27	2504	1	2504	252	252	127	1	29	30	242
18	HCE4G61	209745 04/07/98	Uni-ZAP XR	28	1866	1	1866	130	130	128	1	23	24	285
18	HCE4G61	209745 04/07/98	Uni-ZAP XR	108	1779	1	1720	125	125	208	1	20	21	81
19	HCWUI13	209745 04/07/98	ZAP Express	29	1501	1	1501	80	80	129	1	18	19	157
20	HDPSP01	209745 04/07/98	pCMVSPORT 3.0	30	1752	1	1752	227	227	130	1	20	21	308
21	HHPEN62	209746 04/07/98	Uni-ZAP XR	31	2152	141	2152	183	183	131	1	27	28	508

cgttatgggt	tgaagtaatc	cggactagcg	cagccggggt	taaacgcagg	cttcctgatt	600
gcctgggagg	cctgttcata	cccgtaggcg	accgacagca	acgtggcttc	gctcaaattt	660
ttcccataga	agtgaacggc	tgtcggcatc	ccttcgtcgt	ccatgcccga	tggtatggag	720
ataccgggat	aaccggccac	cgcgagtag	tagtaactgt	atgagtgaag	gttgacatc	780
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agcatctgtt	gatccggcac	acccggaccg	ctgttgcgct	cgttgaattc	aatcagctca	960
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acggcggtata	accgatgcgc	ttgcccacca	aggcgctcagg	cttgattccc	tggtgttagc	1260
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tgccacacgt	gtcctggcgg	gaactgggtca	tcacccttcg	gtactcacta	atccttcgggt	1380
cggtttgaaa	ccaataaacac	cgttgtaagc	cgccggcgta	atgattgaac	cattgggttc	1440
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g						1501

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cagagagtgc	120
attccagccc	180
gggcagcaca	240
gttcttctgt	300
ggggcctcag	360
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cctgcagaca	480
tgtggmtgtc	540
tggaggagca	600
cgtgctctcc	660
tgctgcctct	720
tgccctaggg	780
caaccacaca	840
ctgctggggc	900
gaatgtctct	960
cccaaaaccc	1020
agacctgggt	1080
aacatctgcc	1140
ctgcgactgc	1200
gcggcactgt	1260
tcctggggaga	1320
aacctctgtg	1380
gactccctgg	1440
aacagatccc	1500
acgagggcag	1560
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aagcgtctgg	1680
ccttctcaaa	1740
gggggcggcc	1752

<210> 31  
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<210> 130  
 <211> 309  
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 <213> Homo sapiens

<220>  
 <221> SITE  
 <222> (87)  
 <223> Xaa equals any of the naturally occurring L-amino acids

<220>  
 <221> SITE  
 <222> (185)  
 <223> Xaa equals any of the naturally occurring L-amino acids

<220>  
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 <222> (309)  
 <223> Xaa equals stop translation

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                   20                  25                  30  
 Cys Ser Pro Gly Leu Ser Cys Arg Leu Trp Asp Ser Asp Ile Leu Cys  
                   35                  40                  45  
 Leu Pro Gly Asp Ile Val Pro Ala Pro Gly Pro Val Leu Ala Pro Thr  
                   50                  55                  60  
 His Leu Gln Thr Glu Leu Val Leu Arg Cys Gln Lys Glu Thr Asp Cys  
           65                  70                  75                  80  
 Asp Leu Cys Leu Arg Val Xaa Val His Leu Ala Val His Gly His Trp  
                   85                  90                  95  
 Glu Glu Pro Glu Asp Glu Glu Lys Phe Gly Gly Ala Ala Asp Leu Gly  
                   100                  105                  110  
 Val Glu Glu Pro Arg Asn Ala Ser Leu Gln Ala Gln Val Val Leu Ser  
                   115                  120                  125  
 Phe Gln Ala Tyr Pro Thr Ala Arg Cys Val Leu Leu Glu Val Gln Val  
           130                  135                  140  
 Pro Ala Ala Leu Val Gln Phe Gly Gln Ser Val Gly Ser Val Val Tyr  
           145                  150                  155                  160  
 Asp Cys Phe Glu Ala Ala Leu Gly Ser Glu Val Arg Ile Trp Ser Tyr  
                   165                  170                  175  
 Thr Gln Pro Arg Tyr Glu Lys Glu Xaa Asn His Thr Gln Gln Leu Pro  
                   180                  185                  190  
 Asp Cys Arg Gly Leu Glu Val Trp Asn Ser Ile Pro Ser Cys Trp Ala  
           195                  200                  205  
 Leu Pro Trp Leu Asn Val Ser Ala Asp Gly Asp Asn Val His Leu Val  
           210                  215                  220  
 Leu Asn Val Ser Glu Glu Gln His Phe Gly Leu Ser Leu Tyr Trp Asn

225                      230                      235                      240  
 Gln Val Gln Gly Pro Pro Lys Pro Arg Trp His Lys Asn Leu Thr Gly  
                                  245                      250                      255  
 Pro Gln Ile Ile Thr Leu Asn His Thr Asp Leu Val Pro Cys Leu Cys  
                                  260                      265                      270  
 Ile Gln Val Trp Pro Leu Glu Pro Asp Ser Val Arg Arg Thr Ser Ala  
                                  275                      280                      285  
 Pro Ser Gly Arg Thr Pro Ala His Thr Arg Thr Ser Gly Lys Pro Pro  
                                  290                      295                      300

Asp Cys Asp Cys Xaa  
 305

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 <220>  
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 <223> Xaa equals stop translation

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                                   20                                  25                                  30  
 Pro Ala Leu Leu Glu Lys Val Phe Gln Tyr Ile Asp Leu His Gln Asp  
                                   35                                  40                                  45  
 Glu Phe Val Gln Thr Leu Lys Glu Trp Val Ala Ile Glu Ser Asp Ser  
                                   50                                  55                                  60  
 Val Gln Pro Val Pro Arg Phe Arg Gln Glu Leu Phe Arg Met Met Ala  
                                   65                                  70                                  75                                  80  
 Val Ala Ala Asp Thr Leu Gln Arg Leu Gly Ala Arg Val Ala Ser Val  
                                   85                                  90                                  95  
 Asp Met Gly Pro Gln Gln Leu Pro Asp Gly Gln Ser Leu Pro Ile Pro  
                                   100                                  105                                  110  
 Pro Val Ile Leu Ala Glu Leu Gly Ser Asp Pro Thr Lys Gly Thr Val  
                                   115                                  120                                  125  
 Cys Phe Tyr Gly His Leu Asp Val Gln Pro Ala Asp Arg Gly Asp Gly  
                                   130                                  135                                  140  
 Trp Leu Thr Asp Pro Tyr Val Leu Thr Glu Val Asp Gly Lys Leu Tyr  
                                   145                                  150                                  155                                  160  
 Gly Arg Gly Ala Thr Asp Asn Lys Gly Pro Val Leu Ala Trp Ile Asn  
                                   165                                  170                                  175  
 Ala Val Ser Ala Phe Arg Ala Leu Glu Gln Asp Leu Pro Val Asn Ile  
                                   180                                  185                                  190